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EXAMINER	
BOWMAN, AMY HUDSON	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/665,951	MCSWIGGEN ET AL.
	Examiner	Art Unit
	Amy H. Bowman	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,38,44-52 and 56-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,38,44-52 and 56-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 4/2/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 10/2/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Claims 36, 38, 44-52 and 56-59 are pending in the application.

Applicant's arguments and/or amendments filed on 4/2/07, with respect to the specification objection, claim objection, rejections under 35 U.S.C. 112, second paragraph and rejections under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the instant amendments.

Priority

It is noted that the instant claims are accorded an effective filing date of 3/11/2002, as explained in the office action mailed on 10/2/06.

Claim Objections

It is noted that claim 49 stands objected to because of the following informalities: Claim 49 does not end with a period. Appropriate correction is required. Applicant did not respond to this objection.

Response to arguments- 35 U.S.C., first paragraph

Claims 36, 38, 44-52 and 56-59 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record as explained in the office action mailed on 10/2/2006. Newly added claims 57-59 are rejected for the same reasons.

Applicant has cancelled claims 37, 39-43, and 53-55, thereby obviating the rejection against these claims.

Applicant asserts that all that is required for satisfaction of the enablement requirement is that the specification describe the invention in such terms as to enable one skilled in the art to make and use the invention. Applicant states that the test of enablement is whether one could make or use the invention without undue experimentation. In the instant case, due to the unpredictability in the art regarding successful delivery and action therein of double stranded nucleic acid molecules, one of skill in the art would not be able to predictably make and use the invention.

Applicant further asserts that the test is not whether any experimentation is needed, but whether if experimentation is necessary, is it undue. The examiner agrees with this statement. In the instant case, since the invention cannot be predictably practiced due to the unpredictability of delivery of double stranded nucleic acid molecules and effective action therein, as explained above, the level of experimentation that is necessary is considered undue.

Applicant asserts that the specification teaches the instant method, the structural characteristics of the molecules to be used in the method and how to make the molecules. Applicant relies on the in vivo example in the instant specification of periocular administration of a double stranded nucleic acid molecule and prophetic examples of in vivo delivery and treatment of diseases to demonstrate that the specification teaches one how to use the claimed molecules and methods.

However, as explained in the office action mailed on 10/2/06, this rejection is a scope of enablement rejection. It is acknowledged that applicant is enabled for the in vitro delivery of the claimed molecules and resultant RNA cleavage of SEQ ID NO: 2460 as well as ocular injection of a double stranded nucleic acid molecule in mice with the desired cleavage effect. Although applicant asserts that the office maintains that the specification is not enabling for cleavage of VEGFr1 in vivo despite the teachings of the instant specification, this statement is erroneous. The examiner acknowledges that applicant is enabled for delivery via the means exemplified in the specification, but maintains that applicant is not enabled for the broad scope of the instant claims which encompass any means of delivery for the double stranded nucleic acid molecule.

Applicant asserts that if a particular model is recognized as correlating to a specific condition then it should be accepted as correlated unless the examiner has evidence that the model does not correlate. The basis of this statement in the instant argument is unclear because the examiner is not arguing the correlation of a specific model to any specific condition and this is not an element of the instant claims. The specific mode of delivery exemplified by applicant is not commensurate in scope with the instant claims. Upon a review of the state of the art, effective delivery of double stranded nucleic acid molecules in not considered predictable.

Applicant asserts that the acceptance of therapeutic use of double stranded nucleic acid molecules is further evidenced by the FDA approval of several investigational new drug applications for inhibition of various targets, including VEGFr1. Although applicant has not cited any specific cases to be discussed, it is not being argued that double stranded nucleic acid molecules cannot have therapeutic uses, but rather that the broad scope of delivery of the instant claims is not enabled.

Applicant asserts that that office fails to provide any evidence whatsoever that the instant invention would not work for its intended purposes other than alleging that siRNA technology is an unpredictable art based on the Scherer et al., Mahato et al., and Zhang et al. articles and that applicant has provided ample data and guidance in the specification that demonstrate the efficacy of the instant molecules both in vitro and in vivo.

It is unclear what type of evidence applicant is referring to in the assertion that the office has not provided any evidence whatsoever, because in the same sentence

applicant concedes that the examiner relied upon art regarding the unpredictability of siRNA delivery. The art relied upon by the examiner is the evidence provided by the office to applicant to demonstrate the state of the art regarding unpredictability of delivery of double stranded nucleic acid molecules. Applicant has not argued any of the teachings relied upon by the examiner. Although applicant asserts that applicant has provided ample data and guidance, applicant has not provided ample data and guidance commensurate in scope with the instant claims, which encompass any means of in vivo delivery, which is not enabled.

As outlined above, it is well known that there is a high level of unpredictability in the dsRNA art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely a broad method of cleaving RNA encompassing *in vivo* effects via any means of delivery.

Response to arguments--Claim Rejections - 35 USC § 103

In view of applicant's amendments to the claims, the rejections under 35 U.S.C. 103(a) of record have been withdrawn and a new rejection under 35 U.S.C. 103(a) is below. Applicant's arguments that are pertinent to the instant rejection are addressed below.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36, 38, 44-52, and 56-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 recites that each strand "is 18 to 27 nucleotides in length" in part (b) of the claim. Part (c) of claim 36 recites that the antisense strand "comprises" 18 to 27 nucleotides that are complementary to the target RNA. If the double stranded nucleic acid molecule is closed to 18 to 27 nucleotides in part (b), the antisense strand cannot "comprise" 27 nucleotides that is complementary to the target because the open language of comprising embraces longer fragments. Claims 38, 44-52, and 56-59 are rejected because they depend from claim 36.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36, 38, 44-52, and 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavco et al. (US 6,346,398 B1), in view of Elbashir et al. (The EMBO

Journal, Vol. 20, No. 23, pp. 6877-6888, 2001), Parrish et al. (Molecular Cell, Vol. 6, pp. 1077-1087, 2000), Matulic-Adamic et al. (US 5,998,203), Hammond et al. (Nature, 2001, Vol. 2, pages 110-119), and Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109).

The instant invention is drawn to a method of cleaving RNA comprising SEQ ID NO: 2460 encoded by a mammalian VEGFr1 gene comprising contacting a double stranded nucleic acid molecule with the RNA encoded by the VEGFr1 gene under conditions suitable for the cleavage of RNA, wherein each strand comprises about 18 to about 27 nucleotides and one or more chemical modifications, and one of the strands is complementary to RNA encoded by mammalian VEGFr1 gene and the other strand is complementary to the first strand. The invention is drawn to modifications to the double stranded nucleic acid molecule, terminal cap moieties, and 3' overhangs.

Pavco et al. teach hammerhead ribozymes and antisense oligonucleotides targeted to flt-1, another name for the instantly recited target. Pavco et al. teach chemical modifications including 2'-O-methyl modifications, phosphorothioates, and inverted abasic deoxyribose. Pavco et al. teach that flt-1 is one of the most abundant VEGF receptors and that VEGF expression has been associated with several pathological states such as tumor angiogenesis and rheumatoid arthritis. Pavco et al. teach that targeting and inhibiting flt-1 would beneficially decrease VEGF expression since VEGF exerts its influence by binding to cell surface receptors. Pavco et al. teach compositions comprising the ribozyme or antisense oligonucleotide in a diluent, such as sterilized water.

Pavco et al. do not teach double stranded nucleic acid molecules, 2'-deoxy-2'-fluoro modifications, or terminal phosphate groups.

Elbashir et al. teach dsRNA duplexes 21-23 nucleotides in length with 2 nt 3' overhangs, wherein the overhangs are 2'-deoxy-thymidines. Elbashir et al. teach duplexes with 3' overhangs, as well as duplexes with blunt ends wherein the sense and antisense strand are 100% complementary (see figure 1). Elbashir et al. teach 2'-deoxy and 2'-O-methyl modifications to one or both strands. Elbashir et al. teach that substitution of the 2 nt 3' overhangs by 2'-deoxynucleotides had no effect and even the replacement by two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Elbashir et al. teach a terminal phosphate group.

Parrish et al. teach 26 bp siRNA duplexes that mediate RNAi. Parrish et al. teach modified double stranded RNA molecules comprising a first nucleotide sequence with complementarity to a target and a second nucleotide sequence with complementarity to said first nucleotide sequence. One or both strands comprise modifications. Each strand of the dsRNA molecules taught by Parrish et al. comprises about 18 to about 27 nucleotides, more specifically 26 nucleotides or longer. Parrish et al. teach 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand (see figure 5). Parrish et al. is being relied upon for the teaching of chemical modifications to long dsRNA that was necessarily cleaved into modified siRNA duplexes.

Matulic-Adamic et al. teach incorporation of chemical modifications at the 5'

and/or 3' ends of one or both strands of ribozymes. The 3'-cap taught by Matulic-Adamic et al. is taught to protect the nucleic acids from exonuclease degradation, resulting in increased half-life of the nucleic acid inside of a cell and improved overall effectiveness of the nucleic acid. Additionally, Matulic-Adamic et al. teach various modifications to the base, sugar and/or phosphate to promote stability. Specifically, phosphorothioates and 2' modifications such as H, O-alkyl, C-alkyl, halo and NHR are taught. The ribozymes taught by Matulic-Adamic et al. comprise ribonucleotides and cleave other separate RNA molecules in a nucleotide base sequence-specific manner. Such enzymatic RNA molecules are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. The modifications can be in one or both of the strands. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Hammond et al. teach two methods for silencing specific genes, antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from questionable specificity and incomplete efficacy (see page 110, column 1). Hammond et al. teach that dsRNAs have been shown to inhibit gene expression in a sequence-specific manner and that RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression.

Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy

and reduced non-antisense-related toxicity. Olie et al. added chemical modifications to ribonucleotides at either of the two ends of an oligonucleotide sequence, or the center region together with different combinations of phosphodiester/phosphorothioate backbones and investigated the effect on the activity of antisense oligonucleotides. The gapmer oligonucleotide exhibited a potent bispecific antisense activity. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides.

It would have been obvious to cleave RNA encoded by a mammalian VEGFr1 gene (SEQ ID NO: 2460) with a siRNA because ribozymes and antisense oligos had been previously successfully targeted to the same gene to decrease VEGFr1 expression, as taught by Pavco et al. It would have been obvious to incorporate a terminal phosphate into the siRNA duplex because Elbashir et al. teaches that a terminal phosphate is necessary for activity. It would have been obvious to incorporate a combination of modifications, as taught by Olie et al. and Matulic-Adamic et al.

Furthermore, it would have been obvious to modify the dsRNA duplexes with 2'-O-methyl modifications, phosphorothioates, and inverted abasic deoxyribose, as taught by Pavco et al. and Matulic-Adamic et al., 2'-deoxy and 2'-O-methyl modifications to one or both strands, as well as 3' overhangs of 2'-deoxy-thymidines, as taught by Elbashir et al., or 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al. and Matulic-Adamic et al.

One would have been motivated to use a siRNA targeted to VEGFr1 comprising SEQ ID NO: 2460 instead of an antisense oligonucleotide or ribozymes, as taught by Pavco et al. because Hammond et al. teach that using dsRNA to inhibit gene expression is a sequence specific and potent method, requiring only a few molecules of dsRNA per cell to inhibit the expression of a target gene. Pavco et al. teach inhibition of the instantly recited target and it was known in the art at the time the invention was made that using siRNA duplexes instead of antisense oligonucleotides is preferred, as evidenced by Hammond et al.

Additionally, one would have been motivated to incorporate each of the above mentioned modifications, since each of the modifications were known to enhance the activity of sequence specific inhibitors of target gene expression. The modifications were each known in the art, as evidenced by the modified antisense oligonucleotides and ribozymes taught by Pavco et al., modified siRNA duplexes taught by Elbashir et al., modified dsRNA molecules taught by Parrish et al., and modified ribozymes taught by Matulic-Adamic et al. One would be motivated to maximize a double stranded nucleic acid by incorporating each of the modifications that were known in the art. Olie et al. and Matulic-Adamic et al. teach combinations of modifications to sequence specific inhibitors of target gene expression. One would be motivated to test modifications that are known to benefit oligonucleotide delivery and apply each of them to a dsRNA duplex in order to optimize delivery of the duplex.

Although each of the compounds cited are not specifically siRNA duplexes, each of these molecules were known to face the same delivery challenges. Double stranded

nucleic acid molecules encounter similar problems as other nucleic acid based therapies, and therefore, supports the examiner's position that one would be motivated to incorporate each of the instant modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

Furthermore, Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. teach that combinations of different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Olie et al. teach stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Olie et al. is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations and different configurations, as taught by Olie et al., into the double stranded nucleic acid molecules that were synthesized by Elbashir et al. (EMBO).

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to oligonucleotides. One would expect for such modifications to benefit siRNA duplexes, as each had shown to benefit either siRNA duplexes or other oligonucleotides such as antisense oligonucleotides or ribozymes. One would have a reasonable expectation of success to specifically target a mammalian VEGFr1 comprising SEQ ID

NO: 2460 with a siRNA because it was known in the art that this gene could be successfully inhibited with oligonucleotides, as evidenced by Pavco et al. and that siRNA duplexes are preferred inhibitory molecules, as evidenced by Hammond et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to pertinent arguments--Claim Rejections - 35 USC § 103

Applicant asserts that the office states that Elbashir et al. teaches complete substitution of one or both strands but fails to note that Elbashir teaches away from such molecules. It is noted that the examiner did not note that Elbashir teaches away from such molecules because Elbashir et al. does not teach away from the instant invention. Elbashir et al. teaches that 100% substitution of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished RNAi activity. Elbashir et al. teaches successful inhibition wherein 8 out of 42 nucleotides are chemically modified and does not teach any other examples in between. There are no instant claims directed to molecules wherein 100% of one or both strands are modified with 2'-deoxy or 2'-O-methyl modifications and therefore Elbashir DOES NOT teach away from the instant invention. On the contrary, Elbashir offers motivation to incorporate chemical modifications and test different configurations since Elbashir did modify siRNA duplexes and did result in some duplexes that retained activity.

Applicant asserts that the cited references do not teach every element of the claims because none of the references teach or suggest a siRNA molecule that comprises 2'-O-methyl and 2'-deoxy-2'-fluoro modifications. It is noted that this is not a rejection under 35 U.S.C. 102, but rather 35 U.S.C. 103 and therefore the elements can be taught in the combination of the references rather than every element in the same reference. Furthermore, the instant claims are not directed to "siRNA" molecules, as being argued by applicant.

Applicant further asserts that none of the art, alone or in combination, provides any insight into whether such highly modified double stranded siRNA nucleic acid constructs would function. Contrary to applicant's assertion, Elbashir et al. teach chemically modified siRNA molecules that retain siRNA activity when modified at 19% of the nucleotide positions and Parrish et al. teach extensively modified dsRNA molecules that retained RNAi activity. Applicant asserts that Parrish teaches away from highly modified siRNA constructs and points to figures 5 and 6 of Parrish. Upon a review of figure 5 of Parrish et al., Parrish et al. teach 2'-fluoro modifications in the sense or antisense strand and resultant interference. Therefore, applicant's assertion that Parrish et al. teach away from highly modified double stranded nucleic acid molecules is erroneous.

Applicant asserts that there is no suggestion or motivation to combine the references because Pavco does not teach modification of a single stranded antisense molecule or a ribozyme into a double stranded siRNA molecule. As noted above, the instant claims are not directed to "siRNA" molecules, as being argued by applicant.

Additionally, this is not a rejection under 35 U.S.C. 102, but rather 35 U.S.C. 103 and therefore the elements can be taught in the combination of the references rather than every element in the same reference. The examiner has not asserted that Pavco suggests a siRNA molecule rather than a single stranded antisense oligo or a ribozyme, but rather that one would have been motivated to use a siRNA targeted to VEGFr1 comprising SEQ ID NO: 2460 instead of an antisense oligonucleotide or ribozymes, as taught by Pavco et al. because Hammond et al. teach that using dsRNA to inhibit gene expression is a sequence specific and potent method, requiring only a few molecules of dsRNA per cell to inhibit the expression of a target gene. Pavco et al. teach inhibition of the instantly recited target and it was known in the art at the time the invention was made that using siRNA duplexes instead of antisense oligonucleotides is preferred, as evidenced by Hammond et al. It is the combination of these references that are relied upon by the examiner.

Applicant asserts that Pavco teaches away from modifying the antisense or ribozyme to another structure such as a chemically modified double stranded siRNA molecule because Pavco reported the successful inhibition of flt-1 using a single-stranded antisense molecule or a ribozyme. Simply because Pavco teaches successful inhibition of flt-1 with chemically modified single stranded antisense molecules or ribozymes does not mean that Pavco teaches away from using another type of oligonucleotide agent such as double stranded siRNA that was known in the art to have benefits to single stranded oligonucleotides, as taught by Hammond. Each of these structures are sequence specific inhibitors of target gene expression and double

stranded nucleic acid molecules were known to be potent inhibitors, as evidenced by Hammond.

Applicant asserts that none of the other references even mention the VEGFr1 gene and thus provide no motivation to target VEGFr1 using siRNA. Pavco is the reference that was relied upon by the examiner that teaches targeting VEGFr1 with sequence specific inhibitors of gene expression. The other references do not need to mention this target gene because they are not being relied upon for teachings specific to any gene. Each of these types of molecules including single stranded antisense oligonucleotides, ribozymes, and double stranded molecules including siRNA molecules are known to inhibit the expression of any target gene, given that the sequence is known. Pavco not only teaches sequence specific inhibitors of the same gene that is instantly being claimed but teaches reasoning of why one would desire to inhibit the expression of this specific gene. One would certainly be motivated to use other sequence specific inhibitors such as double stranded RNAs that are known to utilize the same modifications and to be potent inhibitors, as evidenced by Elbashir and Parrish.

Applicant argues that in the time period of about 2000-2001 the high potency of siRNAs as compared to antisense and ribozymes tended to suggest that no additional chemical modification would be necessary. Contrary to applicant's assertion, double stranded nucleic acid molecules are known to face very similar delivery challenges as other sequence specific inhibitors of target gene expression. Furthermore, Elbashir et al. and Parrish et al. are evidence that it was known in the art to chemically modify

double stranded RNA molecules with the same types of modifications that had previously been used in antisense oligonucleotide or ribozyme art.

Applicant points to Elbashir (EMBO) and concludes that emphasis was placed on modifying the 3' single stranded ends rather than the 5' ends. Regardless of what region of the duplex was successfully modified by Elbashir, Elbashir incorporated chemical modifications and resulted in active duplexes. Applicant points to Elbashir II (Methods) and concludes that additional modifications are unnecessary for effective RNAi activity. Simply because Elbashir et al. teach siRNA duplexes that are terminally modified or that do not contain chemical modifications does not mean that one would not have chemically modified double stranded nucleic acid molecules. Again, Parrish et al. and Elbashir et al. each teach chemically modified dsRNA molecules that maintained interference activity with the same types of chemical modifications that were known in the art to benefit sequence specific inhibitors of gene expression.

Applicant further asserts that that Elbashir et al. expressly teaches away from highly modified siRNA constructs based on a passage from "The siRNA User Guide" section of Elbashir et al. It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished RNAi activity. However, there are not any instantly pending claims that are directed to siRNA molecules with these specific structural characteristics and therefore Elbashir et al. do not teach away from the instant claims.

Applicant asserts that because the only teaching in Elbashir addressing the issue of the degree of modifications tolerated in siRNA molecules expressly states that more

than a few end modifications should be avoided, it could not have been obvious to make the highly modified constructs now being claimed. Applicant's interpretation regarding the passage in the Elbashir et al. reference is considered erroneous. Elbashir et al. does not expressly state that more than a few end modifications should be avoided. Elbashir et al. teach chemical modification of siRNA duplexes with 2'-deoxy or 2'-O-methyl modifications and teach modification of 19% of the nucleotides with 2'-deoxy modifications with successful RNAi activity. Elbashir et al. teach that 100% modification of one or both strands abolished activity. This 100% modification is the modification that is being referred to by Elbashir et al. in the passage cited by applicant referring to "more extensive" modification of siRNAs. Elbashir et al. is silent to any modification percentages between the successful example and the loss of activity at 100% and is silent to any other types of chemical modifications at any percentage. Therefore, applicant's assertion that Elbashir suggests that "substantial" modification will destroy RNAi activity is incorrect. Elbashir teaches substantial modification that resulted in RNAi activity and only teaches away from 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications, of which there are no pending claims directed to.

Applicant further asserts that the present claims go directly against the express teachings in the art because there was no reasonable expectation of success in using chemically modified siRNA molecules with 2'-O-methyl and 2'-fluro modifications, based on the teachings of Elbashir et al. Contrary to applicant's assertion, there is an expectation of success given that Elbashir et al. teach that 8 out of 42 nucleotides substituted with 2'-deoxy or 2'-fluoro modifications resulted in successful interference

and these modifications were known in the art to benefit antisense oligonucleotides or ribozymes. One would have been motivated to enhance and optimize the activity of the molecule by incorporating each of the known beneficial chemical modifications.

However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Applicant argues that a reference cited to demonstrate obviousness must be analogous art and asserts that Pavco is not analogous art. Applicant asserts that Pavco is not reasonably pertinent to chemically modified siRNA molecules that target VEFGr1 although Pavco teaches targeting the same target with chemically modified antisense oligonucleotides and ribozymes. Applicant further asserts that the office has conflated ribozyme and siRNA technology into nucleic acid technology and that the office has not offered a teaching that chemical modifications employed in ribozyme technology could be freely and without limitation used in the siRNA technology of Elbashir with a reasonable expectation of success of yielding an active and useful siRNA construct.

Contrary to applicant's arguments, antisense oligonucleotides, ribozymes and double stranded nucleic acid molecules are certainly considered analogous art. Each of the molecules inhibits target gene expression in a sequence specific manner. Each of

the molecules is recognized as facing the same delivery challenges. The same exact chemical modifications have been used with siRNA molecules and dsRNA molecules as had been used with antisense oligonucleotides or ribozymes in order to enhance the activity of each of these molecules. This is evidenced post-filing by the teachings of Elbashir et al. and Parrish et al., each of which modified dsRNA molecules with chemical modifications that were known in the art to benefit other types of nucleic acid technology that mediate inhibition of target gene expression in a sequence specific manner. Pavco teaches using antisense oligonucleotides or ribozymes with chemical modifications to target and inhibit the same target gene that is instantly recited and Hammond teaches the benefit of double stranded RNA molecules.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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